A critical role for AID in the initiation of reprogramming to induced pluripotent stem cells.

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Public Summary:
Reprogramming of somatic cells to generate induced pluripotent stem cells (iPSCs) has unprecedented potential for regenerative medicine, for cell-based therapies, for modeling human diseases in culture, and for drug discovery. Our study shows that AID (activation-induced deaminase) is a common early regulator not only in cell fusion-based reprogramming but also in reprogramming to iPSCs. We postulate that an identification of such early regulators will not only increase our understanding of the mechanisms underlying reprogramming but also increase the efficiency of iPSC generation.

Scientific Abstract:
Mechanistic insights into the reprogramming of fibroblasts to induced pluripotent stem cells (iPSCs) are limited, particularly for early acting molecular regulators. Here we use an acute loss of function approach to demonstrate that activation-induced deaminase (AID) activity is necessary for the initiation of reprogramming to iPSCs. While AID is well known for antibody diversification, it has also recently been shown to have a role in active DNA demethylation in reprogramming toward pluripotency and development. These findings suggested a potential role for AID in iPSC generation, yet, iPSC yield from AID-knockout mouse fibroblasts was similar to that of wild-type (WT) fibroblasts. We reasoned that an acute loss of AID function might reveal effects masked by compensatory mechanisms during development, as reported for other proteins. Accordingly, we induced an acute reduction (>50%) in AID levels using 4 different shRNAs and determined that reprogramming to iPSCs was significantly impaired by 79 +/- 7%. The deaminase activity of AID was critical, as coexpression of WT but not a catalytic mutant AID rescued reprogramming. Notably, AID was required only during a 72-h time window at the onset of iPSC reprogramming. Our findings show a critical role for AID activity in the initiation of reprogramming to iPSCs.